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A new biomarker for early diagnosis in patients with sepsis in intensive care units: presepsin

Yoğun bakım ünitelerinde sepsisli hastalarda erken tanı için yeni bir biyobelirteç: presepsin

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ABSTRACT

Introduction/Aim: Today, sepsis is the most common cause of death in intensive care units. In this study, we aimed to compare presepsin with procalcitonin (PCT) and C-reactive protein (CRP) which are commonly used in the early diagnosis and treatment of sepsis.

Material and Method: One hundred-eighty three patients who were hospitalized in the Intensive Care Unit were included in the study. While 138 of these patients were followed with the diagnosis of sepsis, 45 were hospitalized in the intensive care unit for reasons other than sepsis. Blood, urine, stool and tracheal aspirate cultures were obtained from these patients. Simultaneous procalcitonin, CRP and presepsin levels were measured. Quick Sequential Organ Failure Assesment (QSOFA) and Acute Physiology and Chronic Health Assessment-II (APACHE-II) scores were calculated. The data obtained were analyzed statistically by SPSS (Statistical Package for Social Sciences) 20.0 package program.

Findings: 45.5% of the patients were female and the mean age of the patients was 75.74±11.35. Patients had concomitant chronic diseases, 14% of patients had diabetes mellitus, 45% had hypertension, 54% had renal failure and 26% had chronic obstructive pulmonary disease. No significant relationship was found between the levels of presepsin and the patients with septic and non-septic patients ($p>0.05$). However, a strong positive correlation was found between elevated presepsin levels and CRP levels ($r=0.853$; $p<0.001$).

Conclusion: As a result of the study, no significant difference was found between presepsin levels of patients with and without sepsis, while presepsin was a valuable biomarker for early diagnosis of sepsis in culture positive septic patients. It also showed a strong correlation with CRP and PCT, thus it may used in the daily clinical practice of septic patients.

Keywords: Sepsis, intensive care, presepsin, biomarker

ÖZ

Giriş/Amaç: Günümüzde sepsis, yoğun bakım ünitelerinde en yaygın ölüm nedenidir. Bu çalışmada, presepsin ile sepsisin erken tanı ve tedavisinde yaygın olarak kullanılan prokalsitonin (PCT) ve C-reaktif proteinin (CRP) karşılaştırılmasını amaçladık.

Gereç ve Yöntem: Yoğun Bakım Ünitesine yatırılan 183 hasta çalışmaya dahil edildi. Bu hastaların 138'i sepsis tanısı ile takip edilirken, 45'i sepsis dışındaki nedenlerle yoğun bakım ünitesine yatırılmıştı. Bu hastalardan kan, idrar, dışkı ve trakeal aspirat kültürleri alındı. Eş zamanlı prokalsitonin, CRP ve presepsin düzeyleri ölçüldü. Hızlı Sıralı Organ Yetmezliği Değerlendirmesi (QSOFA) ve Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE-II) skorları hesaplandı. Elde edilen veriler, SPSS (Sosyal Bilimler için İstatistiksel Paket) 20.0 paket programı ile istatistiksel olarak analiz edilmiştir.

Bulgular: Hastaların % 45,5'i kadındı ve ortalama yaşları 75,74±11,35 idi. Hastalarda eşlik eden kronik hastalıklar olarak %14'ünde diabetes mellitus, %45'inde hipertansiyon, %54'ünde böbrek yetmezliği ve %26'sında kronik obstrüktif akciğer hastalığı vardı. Presepsin düzeyleri açısından septik ve septik olmayan hastalar arasında anlamlı ilişki bulunmadı ($p>0,05$). Bununla birlikte, yüksek presepsin düzeyleri ile CRP düzeyleri arasında güçlü bir pozitif korelasyon bulundu ($r = 0,853$; $p<0,001$).

Sonuç: Çalışma sonucunda, sepsisli ve sepsisli olmayan hastaların presepsin düzeyleri arasında anlamlı bir fark bulunmadı. Ancak presepsin, kültür pozitif septik hastalarda sepsisin erken tanısı için değerli bir biyobelirteç idi. Ayrıca, CRP ve PCT ile güçlü bir korelasyon gösterdi, bu nedenle septik hastaların günlük klinik pratiğinde kullanılabilir.

Anahtar Kelimeler: Sepsis, yoğun bakım, prepepsin, biyobelirteç

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INTRODUCTION

Sepsis is still responsible for the death of one person every 4 hours in the world and still affects millions. Some studies show that this rate is 65.5/100000 in the USA (1). Although modern antibiotics have been developed and cardiovascular and pulmonary support systems have been improved, patient deaths are increasing due to sepsis in intensive care units (ICU) (2). Therefore, the detection and identification of sepsis have a great importance, but there are still some difficulties in recognizing sepsis. The American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) developed criteria for Systemic Inflammatory Response Syndrome (SIRS) in 1991(3).

According to criterias of SIRS;

i. Temperature should be >38 or <36 °C
ii. Heart rate should be >90 BPM
iii. Respiratory rate should be >20 or paCO2 <32 mmHg per minute
iv. White blood cells should be >12000, <4000 or immature band forms >10%.

In addition, various scoring systems for sepsis have been developed using clinical signs and symptoms in daily practice. Acute Physiology and Chronic Health Assessment-II (APACHE-II) (4), Sequential Organ Failure Assesment (SOFA) and rapid SOFA (qSOFA) (5) are some of them. However, the results of these scores are not effective enough in the early diagnosis of sepsis.

Today, blood culture is still the gold standard in the diagnosis of sepsis, but the time taken for outcomes is quite long (6). This time is valuable for critically ill patients. Therefore, it is inevitable to use biomarkers which result in a shorter time. Therefore, more than 180 biomarkers have been identified to recognize sepsis (7). Among these, C-Reactive Protein (CRP) and Procalcitonin (PCT) have found widespread use in clinical practice for easy accessibility and cost.

C-Reactive Protein (CRP): CRP is the most widely used biomarker in sepsis and is synthesized as an acute phase reactant from the liver (8). However, plasma exchange of CRP is not only associated with the progression of sepsis. In addition, many factors such as acute coronary syndrome, malignancy, obesity, cerebrovascular disease and drugs increase the plasma level of CRP (9).

Procalcitonin (PCT): PCT is an important biological marker that has recently entered clinical practice. Studies have shown that it is more susceptible than CRP (10). However, there is false positivity in cases of multiple trauma and severe burns (11) PCT secretion is increased by microbial toxins and bacterial-specific mediators (IL-1β, TNF-α and IL-6) and decreased in viral infections in which IF-γ is released.

Presepsin (sCD14-ST): Presepsin is a biomarker identified in 2004 by proteolytic cleavage of CD14 (12). Lipopolysaccharide (LPS) structure presents for high affinity receptors. When the LPS-CD14 complex is formed, the soluble form becomes detectable in the blood (13).

MATERIAL AND METHOD

The study was carried out subsequent to receiving permission for its conduct from the presiding local Ethics Committee (Permission Granted 30/05/2015, Decision No.35 (2015-60). The study follows the 'Ethics' Standards of the' World Medical Association Helsinki 'Principles' Declaration.

The study was designed as a single-center, prospective study. First of all we performed statistical power analysis. If the true slope of the line obtained by regressing yvar against xvar is 1, we calculated that we will need to study 178 subjects to be able to reject the null hypothesis that this slope equals zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis was 0.05. And then we included in 183 patients hospitalized in the Intensive Care Unit (ICU) of Sultan Abdulhamid Han Training and Research Hospital between 2017-2018 to our study. While 138 of these patients were followed for sepsis, 45 were hospitalized in the ICU for non-sepsis reasons. Informed Consent Forms prepared in accordance with Helsinki Declaration for the study were signed by the patient and / or their relatives.

The diagnosis of sepsis was calculated by APACHE-II and qSOFA scoring systems and divided into two groups with/without sepsis. Blood, urine, stool and tracheal aspirate cultures were obtained from the patients. Reproduction was recorded. In addition, demographic findings such as age and gender of the patients were recorded. In this study, ex patients and discharged patients were listed as ex/discharged. Simultaneous biomarkers and biochemical parameters were also recorded. Blood samples for Presepsin from biomarkers were centrifuged and stored at -80 °C until they were delivered to the center where the measurements would be taken. We used human presepsin kit that the kit is a sandwich enzyme immunoassay for in vitro quantitative measurement of presepsin (PSPN) in human serum, plasma, tissue homogenates and other biological fluids (Biont, Catalog No: YLA1410HU 96 Test PSPN Human ELISA Kit).

Statistical Analysis

The data obtained were analyzed statistically by SPSS (Statistical Package for Social Sciences) 20.0 package program. Kolmogorov Smirnov test was used to determine

whether the data fit within the normal distribution. Pearson/Spearman correlation was used to determine the relationship between number and percentage mean, and Mann-Whitney U test was used to compare independent variables. Statistical significance was accepted as p <0.05 in all analyzes.

RESULTS

41.5% of the patients included in our study were female and 58.5% were male patients. Overall age of the study was found to be 75.74 ± 11.35 years. Chronic disease conditions are given in **Table 1**. Accordingly, 14% of patients had Diabetes Mellitus (DM), 45% had hypertension (HT), 54% had renal failure (RF) and 26% had chronic obstructive pulmonary disease (COPD).

Table 1. Demographic characteristics and chronic disease status of patients

	Mean	SD	Min.	Max.
Age (year)	75.74	11.35	34	93
Gender	Female		Male	
	76		107	
	(+)		(–)	
DM	27		156	
HT	84		99	
RF	96		87	
COPD	48		135	

COPD: Chronic obstructive pulmonary disease

As a result of the examinations performed in the patients included in the study, no significant relationship was found between the level of presepsin and the patients with sepsis and inpatients in the ICU for non-sepsis reasons (p>0.05).

Presepsin levels of patients with sepsis and culture growth were significantly higher than those without culture growth (p=0.002). At the end of the study, no significant relationship was found between presepsin levels of ex-patients and discharged patients (p>0.05) (**Table 2**).

Table 2. Comparison of presepsin values according to the presence of sepsis, culture growth and discharge status

	Presepsin			
	n	Mean Rank	Z	p
Sepsis (+)	144	94.29	- 1.123	0.261
Sepsis (-)	39	83.55		
Culture growth (+)	119	100.99	- 3.131	0.002
Culture growth (-)	64	75.28		
Sepsis & Culture growth (+)	93	101.23	-2.395	0.017
Discharged patients	54	64.25	- 0.981	0.327
Ex-patients	129	74.15		

In patients with sepsis, a strong positive correlation was found between elevated presepsin levels and CRP levels (r=0.853; p<0.001). There was also a strong positive correlation between the levels of presepsin and PCT levels of the same patient group (r = 0.649; p <0.001) (**Table 3**).

Table 3. Relationship between presepsin and procalcitonin and C-reactive protein

	r	p
CRP	0.649	<0.001
PCT	0.853	<0.001

When the relationship between presepsin levels and APACHE-II and qSOFA scores of the patients was examined, no significant difference was found (p> 0.05) (**Table 4**).

Table 4. Relationship between presepsin and APACHE-II and qSOFA scores

	r	p
APACHE-II	0.052	0.485
qSOFA	0.055	0.458

DISCUSSION

Our main aim in this study was to show that Presepsin is a more sensitive and more specific biomarker for the early diagnosis of sepsis patients in ICU.

Today, many biomarkers are used solely or in combination to determine the early diagnosis, prognosis and mortality of sepsis (14).

In a study conducted by Godnic et al. (15) in 2015, presepsin levels were found to be significantly higher in patients with sepsis hospitalized in the ICU, but in our study, no significant difference was found between the patients with and without sepsis in the ICU. However, presepsin levels were found to be significantly higher in septic patients with culture growth than in septic patients without culture growth. In this context, considering the fact that culture is still the gold standard in the diagnosis of sepsis; since the time taken for growth in culture is critical in the diagnosis and prognosis of the patient, the high levels of presepsin will guide us in the early diagnosis of sepsis patients with culture reproduction.

In a study published by Kweon et al. (16) in 2014, presepsin level was shown to be an important biomarker in predicting mortality, but in our study, no significant difference was found between presepsin levels of ex and discharged patients from the ICU. Liu and colleagues found that presepsin showed a significant association with biomarkers used in sepsis such as CRP and PCT (17). In our study, positive correlations were found between presepsin and CRP, and presepsin and PCT in

patients with sepsis. This showed that presepsin can be used together with biomarkers that are used currently to determine the diagnosis and prognosis of sepsis in practice. As a result, considering the difficulty in the diagnosis of sepsis, it has been thought that using biomarkers in combination is much more beneficial than using them solely.

In a study conducted by Behnes et al. (18), a significant association was found between Presepsin and APACHE-II which is one of the scoring systems used for the diagnosis of sepsis, however no significant difference was found between presepsin and APACHE-II, and presepsin and qSOFA in our study. These different outcomes can be due to the subjective nature of some data in the scoring systems, or because of the duration in the ICU after the diagnosis of sepsis and/or failure to record the data quickly and accurately.

CONCLUSION

As a result of our study, Presepsin may be an important biomarker for early diagnosis of sepsis patients with culture growth in ICU. In the future, more cost-effective, validated, easier and faster accessible presepsin level measurements will become even more important for early diagnosis of sepsis. This can only be demonstrated by larger studies with a higher number of patients.

However, considering that sepsis and the response to sepsis vary widely, it seems difficult to use a single biomarker in the early diagnosis of sepsis in clinical practice. In this case, it is more likely to use more than one biomarker simultaneously.

ETHICAL DECLARATIONS

Ethics Comittee Approval: The study was carried out subsequent to receiving permission for its conduct from the presiding local Ethics Committee (Permission Granted 30/05/2015, Decision No: 35, 2015-60).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

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